CLINICAL RESEARCH MEETING

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MEDICAL DIVISION

BERNARD S. OPPENHEIMER, Presiding Officer

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Effect of Liver Disease on Vitamin A Absorption

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The liver has an important function in the metabolism of Vitamin A. It converts the provitamin carotene into the vitamin and is the chief depot of the latter. Marked changes of Vitamin A metabolism are found in liver disease.

In normal individuals the "fasting" Vitamin A blood level remains constant with normal nutrition. In acute hepatitis, cirrhosis of liver and other forms of liver damage, e.g., in mechanical obstruction with superimposed parenchymal damage, the blood Vitamin A figures are low and return gradually to the normal level in the recovery phase. There exists, however, no strict parallel between the extent of hepatic damage, as evaluated by the various liver function tests (blood cholesterol, esterified cholesterol, galactose tolerance, cephalin flocculation, prothrombine time, icterus index, etc.) and the lowering of the Vitamin A level.

The response to the oral administration of a test dose of Vitamin A (Vitamin A Tolerance Test) was studied in 50 cases of liver disease and many controls. In partial biliary obstruction (stone, neoplasm) and in compensated cirrhosis the response is usually normal. In acute hepatitis, cirrhosis with superimposed hepatitis, and in prolonged biliary obstruction, the postprandial elevation of Vitamin A in the blood is reduced or completely absent. The character of the curves varies with the nature of the hepatic disease, the stage of the disease, and the extent of hepatic damage. Evidence is accumulating that the flat curves in liver disease are caused by impaired intestinal absorption and perhaps by depletion of Vitamin A reserves in the liver. In the recovery stage normal or even abnormally high curves are observed, suggesting satisfactory intestinal absorption but insufficient deposition in the liver.

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A Qualitative Change in Serum Albumin in Parenchymal Liver Disease

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Kabat et al., in 1943, reported studies on the reaction of cephalin-cholesterol emulsions and colloidal gold suspensions with various fractions of normal and pathological sera as obtained by electrophoretic separation and showed (1) gamma globulin from normal

and pathological sera (parenchymal liver disease) causes comparable flocculations, whereas no other protein component of the serum gives the flocculation reaction and (2) normal albumin inhibits the colloidal gold reaction with gamma globulin but not the cephalin flocculation. The purpose of this paper is to report further investigation of electrophoretically separated protein fractions from the sera of normal persons and of sera from patients with parenchymal liver disease, over a wider range of concentrations than those used by Kabat and his collaborators.

The investigation was conducted using the sera from 2 patients (catarrhal jaundice and arsphenamin hepatitis) and 1 normal subject. The cephalin flocculation was done as described by Hanger using varying amounts of protein components. Separation of the protein fractions was carried out in the Tiselius apparatus and the concentration of each fraction determined by measuring its refractivity in a previously calibrated Zeiss interferometer.

The procedure followed was:

1. Knowing that an excess of normal serum inhibits flocculation of abnormal serum, the range at which complete inhibition occurs was established.

2. The concentration of the various protein fractions within the effective inhibiting range was determined.

3. We were then able to duplicate the conditions of inhibition using amounts of either normal albumin or abnormal albumin comparable to the albumin in the inhibiting serum, against amounts of gamma globulin comparable to the gamma globulin in the flocculating serum.

It was found that normal albumin inhibits completely the flocculation of gamma globulin in the proportions used, whereas identical amounts of albumin from cases of parenchymatous liver disease showed little if any inhibiting properties. Table II.

The albumin from all sources showed no flocculating properties. We have further confirmed the findings of Kabat et al that the gamma globulin in health and liver disease shows identical flocculating capacities. Table I.

The evidence presented points to qualitative changes in the albumin fraction in parenchymatous liver disease in that the inhibiting properties of normal albumin are not observed in this abnormal albumin. It is significant that crystallized normal human serum albumin fails to inhibit the flocculation of gamma globulin. The nature of these changes is now under investigation.

TABLE I—EFFECTS OF VARIOUS SERUM COMPONENTS ON THE CEPHALIN FLOCCULATION REACTION

	Normal Patient	*Hepatitis Patient*
Whole serum	0	++++
WSerum albumin.	0	0
Serum gamma globulin.....	++++	++++

TABLE II—THE INHIBITING POWERS OF ALBUMIN FROM NORMAL SERUM AND HEPATITIS SERUM IN THE FLOCCULATION OF GAMMA GLOBULIN

	Gamma globulin in diminishing amounts				
	0.1	0.08	0.06	0.04	0.02
No serum albumin added.....	++++	++++	+++	++	0
Albumin from normal serum added.....	0	0	0	0	0
Albumin from hepatitis serum added.....	+++	+++	+	0	0

*Nocturnal Secretion Studies in Normals and in Patients with Peptic Ulcer**

ALBERT CORNELL, ASHER WINKELSTEIN and FRANKLIN HOLLANDER

In 1928, Chalfen[1] showed that nocturnal secretion in normal persons was lacking in free hydrochloric acid, or, if present, was only minimal in amount. Winkelstein[2] confirmed these findings and also found a marked increase in the quantity and concentration of free hydrochloric acid in patients with peptic ulcer, especially those with duodenal ulcer. In 1932 and 1933 Henning and Norpoth[3] confirmed these latter observations, as did Val Dez[4] in 1942. Recently, however, Sandweiss[5] and his coworkers reported that both normal subjects and patients with duodenal ulcer secreted acid gastric juice although a greater quantity of juice was aspirated from the patients with ulcer. Because of such opposing views, chiefly with reference to the findings in normals, further studies have been carried out at The Mount Sinai Hospital since 1938. The purpose of this communication is to present these studies.

The normal subjects consisted of 9 males without any history of gastrointestinal disturbances admitted to the hospital for a herniorrhaphy or similar procedure. The older age group was eliminated so as not to introduce possible achlorhydria due to age alone. The patients with peptic ulcer were those with uncomplicated duodenal ulcer, proven by x-ray or operation. In this group there were 16 test meals carried out on 14 patients.

From our studies, we conclude that patients with uncomplicated duodenal ulcer reveal a large amount of highly acid secretion during the night. Normal subjects showed little or no free hydrochloric acid and specimens were difficult to obtain in most instances because of the small amount of night secretion.

* From the Gastro-Enterology Research Laboratory and the Services of Drs. George Baehr, B. S. Oppenheimer and Ralph Colp, Mount Sinai Hospital.

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Cold Hemagglutination and Cold Hemolysis

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The association of cold agglutination of erythrocytes with some cases of non-syphilitic paroxysmal cold hemoglobinuria and hemolytic anemia has been known for years. However, the mechanism by which cold hemagglutination leads to hemolysis had not been elucidated previously.

The studies show that the hemolysis which is dependent upon cold hemagglutination is due jointly to a high titer (over 1/3000) of cold hemagglutinins, a high concentration of erythrocytes in the reacting mixture and mechanical trauma brought about by shaking or tapping. There is a direct linear relationship between the cold hemagglutinin titer and the cold hemolysin titer. Complement action is not necessary for hemolysis. The slightest amount of agitation of strongly agglutinated blood is followed by hemolysis.

Using an apparatus consisting of a 3-foot length of capillary glass tubing immersed in ice water, it is shown that the mechanical trauma due to the injection through this tube of blood containing potent cold hemagglutinin is enough to cause intense hemolysis. Numerous controls of this test have been carried out successfully.

The immersion in cold water of an extremity of a patient whose blood contains potent cold hemagglutinins causes intravascular hemolysis.

Antibody Production After Antigenic Pneumococcic Polysaccharides in Man and in Animals

Relationship Between Nutritional Deficiencies, Contributory Diseases and Resistance to Infection

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To test the antigenic properties of the polysaccharide used in this work[1] a group of mice were injected in the peritoneum with ½ cc. of 1:1,000,000 solution and 8 days later dilutions of pneumococcus culture were injected in the abdominal cavity. Protection was found in 50 per cent of the mice against 1-5,000,000 lethal doses. Since in the mouse-protection tests the animals die of bacteriemia before pneumonia develops, in another set of experiments the question was examined whether the antigen gives protection against experimental pneumonia. Method used was similar to the one of Stillman and Branch:[2] animals were exposed to infection in a closed box sprayed with 10 cc. of virulent pneumococcus solution; pneumonia developed only in 2 per cent of the animals. If, however, they were previously intoxicated with intraperitoneal alcohol injection or with ether inhalation, 20-50 per cent developed pneumonia. Of the animals who received ½ cc. of 1:1,000,000 dilutions of antigen and similarly treated, all except 5 per cent remained healthy.

In the five years 1937-1942 an experiment in which 9,070 individuals were involved was done. Half of them were injected with the antigen and the other half were kept as controls. In the first two years every 20th person was bled before and 14 days after the antigen and the protective antibodies of 0.10 cc. of the sera titrated in mice.

Results: a) Sixty-five per cent of the immunized showed a hundredfold increase of protective bodies; b) in five years the incidence of pneumonia was less than one-half among the immunized as compared to the controls (16.5 per cent against 38.6 per cent); c) the mortality rate was about one-third among the immunized of that of the control group. Since, however, our figures indicate great fluctuation in the number of pneumonias from one year to the other, we believe that this type of experiment permits definite conclusions only if conducted for about 6 to 10 years.

There were indications in our work that those who were not able to manufacture antibodies were more prone to pneumonia infection than the ones who were able to do so. It also seemed that the percentage of negative reactors was considerably higher in the group investigated than in the general population. The next step was to examine the possible causes of this and of the high incidence of pneumonia in institutionalized individuals and among the aged. A survey of nutritional deficiencies was made by study of hospital charts, diets, medical, laboratory and biomicroscopic examinations in both negative and positive reactors. Also a survey was made of the inter-relationship between deficiency states and certain conditioning diseases. Results: a) 93 per cent of the investigated old individuals showed one or more signs of nutritional deficiencies; b) somewhat higher was the prevalence of deficiency states among the negative than positive reactors; c) the relationship between vitamin deficiency states and certain conditions (liver damage, nephrosis, long-standing decompensated heart failure, anemias, achlorhydria, general malnutrition) was suggestive of a reciprocal action, i. e., the diseases are contributory factors in the development of deficiency states and the deficiencies produce or aggravate these diseases. Other than nutritional causes of high incidence of pneumonia in the group investigated were also examined and found probably to be: crowding, presence of carriers, diminished cough reflex, frequency of conditioning diseases and general decline of

the defense mechanism in the aged. At this phase we also investigated the problem whether optimal diet and optimal doses of vitamins increase the ability of the negative reactors to manufacture antibodies in a higher degree than before. The individuals were "vitaminized" for 4 weeks, bled, then pneumococcus polysaccharide was injected and 2 weeks later they were bled again. Both batches of sera were titrated for their mouse protective contents against dilutions of pneumococci. Results: a) there was improvement in a great number of the deficiency signs; b) the protective titer increased only in 3 out of 58, which statistically is not significant.

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The Treatment of Filariasis (Wuchereria Bancrofti) with Anthiomaline

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Recent military medical reports indicate that men in the theaters of war are exposed to filaria infections and a number of them have become infected. The therapy of filariasis has been unsatisfactory but recent therapeutic trials of anthiomaline, an antimony compound, in human filarial infections indicate that this drug may be effective. A number of persons exhibiting *Wuchereria bancrofti* microfilaria in their blood were treated with intramuscular injections of anthiomaline and their microfilaria counts were reduced 85 to 100 per cent. These cases have now been followed for six months without relapses among the group. The toxicity of the drug to man is sufficiently low to warrant its continued trial in the early stage of filaria infection.

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*Clinical Arrest of Bacterial Endocarditis by Bacteriostatic Agents, Particularly Penicillin**

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In the experimental endocarditis of rabbits, induced by intravenous injection of cultures of streptococci of the viridans group, healing and healed lesions of the disease have been observed following the therapeutic use of anti-infectious agents. The early defense against the infection depends chiefly upon phagocytosis and digestion of the bacteria by vascular endothelium and wandering leukocytes. At the sites of more severe injury, as on the heart valves where physical stress and pressure aids the infectious agents, there is deposit of fibrin in which the bacteria may multiply abundantly. Subsequent limitation and healing of these infected thrombotic deposits is favored by (1) bacteriolysis, (2) phagocytosis and (3) encapsulation and scar formation. Restraint of rapid bacterial multiplication is evidently essential to the success of the healing processes and hence there is easily recognized the therapeutic need of (1) physiological rest (2) anti-infectious agents in the circulating blood and (3) adequate nu-

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trition for the defending cells.

Some anti-infectious agents of chemical and of biological origin have shown significant effects upon the bacterial cultures *in vitro* and their use in experimentally infected animals has in some instances been followed by observation of healing and healed lesions of endocarditis. Application of these observations in therapy of the human disease could not be delayed. One example of apparent arrest in which there was a long period of deterioration approaching the terminal stage followed by a successful program of treatment, may be briefly presented at this time.

M. F., female, 32, developed endocarditis following dental extraction on February 22, 1943, with mitral murmur, recurrent petechiae, persistent positive blood cultures, embolic lesions of brain, retinae and spleen, hematuria and extreme emaciation, in spite of treatment with sulfadiazine, thiobismol, neoarsphenamine and multiple small transfusions. A very small supply of partially processed penicillin became available on June 23 and this seemed to have a slight beneficial effect without halting the progressive down-hill course of the disease. However, on September 15 the use of more adequate amounts of penicillin was followed by dramatic clinical improvement. The blood culture taken on September 20 remained sterile as did all subsequent cultures of the blood. Penicillin was continued in doses of 5,000 units every 2 hours, with some variations, until January 7, then reduced to 3,000 units and on January 10 to 1,000 units. It was finally discontinued on January 17. The total penicillin expended was approximately 4,864,000 units. The patient has regained her normal weight and appears well except for persistent moderate weakness of legs, ankles and feet. This does not prevent walking.

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Combined Penicillin and Heparin Treatment of Subacute Bacterial Endocarditis[1]

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A conjoint chemotherapeutic and anticoagulant attack has been effective in causing the disappearance of experimental thrombotic endocarditic lesions.[2] Results with sulfonamides and heparin in human cases of subacute bacterial endocarditis have been disappointing. When penicillin was substituted as the chemotherapeutic agent in the combined treatment the results were striking and consistent.

The dosage schedule for both penicillin and heparin has been worked out. The penicillin was given mostly by continuous venoclysis. The heparin was administered either by a specially devised subcutaneous method[3] or by venoclysis in combination with the penicillin.

Seven out of eight cases in the initial series were successfully treated; that is, the blood stream became bacteria free and the patients exhibited marked, progressive clinical improvement. In contrast with sulfonamides, the treatment has minimal toxicity and is well tolerated. Twenty-two additional patients have been or are being treated with similar promising results.

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Thiouracil in the Treatment of Postoperative Recurrent Toxic Goiter

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Recurrence of toxic goiter after a subtotal thyroidectomy presents a difficult problem in therapy. In many instances further operation is inadvisable, and radiotherapy or iodine may not stop the overactivity of the gland.

The results of thiouracil therapy in a series of 13 cases of recurrent hyperthyroidism of this nature, and 2 more cases of exophthalmos are reported here. These have been successfully treated in the thyroid clinics of the Vanderbilt Clinic and in the Presbyterian Hospital, for more than 4 months at the present time. Toxic symptoms from the drug have been few, but, when present, severe enough to warrant stopping treatment. A fair amount of variability is found in the dosages needed to reduce the basal metabolic rate to normal and to maintain this lowered level. The effect of the drug upon the basal metabolic rate, fasting serum cholesterol, symptoms and physical signs is to restore these to normal. Exophthalmos may progress during thiouracil therapy. Caution in the use of thiouracil and very careful watch over the blood count are necessary in using this treatment.

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The Effect of Certain Liver Extracts on the Carbohydrate Metabolism (Clinical and Experimental Study)

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The question of the effect of liver extract on the carbohydrate metabolism was revived when Blotner and Murphy published in 1929 a paper in which they claimed an insulin like action of liver and liver extract on the blood sugar in the human, and especially in those suffering from diabetes.

Later investigations carried out by a number of workers not only failed to support these claims, but on the contrary it became evident that a definite rise in the blood sugar occurred following the administration of certain liver extracts. This was noted in man as well as in the experimental animal.

Henry B. Sokal's experience with the effect of liver extract on the carbohydrate metabolism in man goes back to the year of 1932. At that time seventeen patients suffering from pernicious anemia were treated by him with an extract supplied for clinical use by the Wilson Laboratories in Chicago.

He used two extracts, fraction "A" and fraction "B." Both were intended for parenteral use, and supplied in individual 5cc. ampules. To test the potency of both fractions the patients were divided into two groups; one group receiving regularly fraction "A," while the other was treated with the fraction "B" extract.

After some weeks of treatment, one patient, a woman about 60 years old, began to complain of a severe and persistent itch in the vulva. Examination of the urine showed the presence of a reducing substance and the blood sugar was 150 mg./100 cc. A blood sugar examination made about six months previously during the patient's stay in the hospital was recorded at 90 mg., and the urine at that time was negative.

Since the coexistence of pernicious anemia and diabetes mellitus was always regarded as a very rare occurrence, he assumed that the liver extract was in some way responsible for the appearance of these changes. To make sure that this was not a mere

coincidence he examined the urines and blood sugars of several other patients who were then under the treatment with this extract. The results of these examinations confirmed his suspicions. All patients treated with the fraction "B" of the extract had glycosuria and an elevated blood sugar. Continuation of the treatment caused a gradual rise in the blood sugar, until after several months of treatment the blood sugar reached the level of 320 mg./100 cc.

In several patients he had the opportunity to determine the level of the blood sugar just before starting them on this extract. After 6-8 injecions with the fraction "B" of the liver extract a 50 per cent increase in the blood sugar was the rule.

His resignation from the clinic postponed further work on this problem until 1937, when Dr. Long of the Yale Medical School was kind enough to extend the facilities of his Department for the experimental study carried out there by his son, Joseph E. Sokal.

As a preliminary to the experimental study six commercial liver preparations were examined for their ability to produce glycosuria and hyperglycemia; no attempt was made to find an extract capable of reducing the blood sugar. A complete chemical study of the extracts was made. In general they were water soluble, free of protein and contained the equivalent of about 14 per cent of glucose. Normal mice, guinea-pigs, and rats were used in these experiments. Studies were also carried out on adrenalectomized rats, on latent diabetic rats and in one frankly diabetic rat.

Daily determinations of urinary glucose over long periods, both during the administration of liver extract and during control periods were made in all animals used in this study. The effect of liver extract on the blood sugar levels was studied during the fasting state as well as in the absorptive and postabsorptive state.

In a number of animals studies were carried out on the effect of insulin on the hyperglycemia produced by the administration of the liver extract. Investigations were also made on the effect of liver extract on the carbohydrate stores in normal animals in the fasting and absorptive state. Other studies made during these experiments were: The effect of liver extract on the nitrogen balance and on the respiratory quotients in normal and diabetic animals in the fasting state and during the absorption of glucose. Finally attempts were made to isolate the glycogenolytic principle.

In the course of these investigations it was proven conclusively that by injection of Wilson's liver extract fraction "A" and "B," glycosuria and hyperglycemia were produced in every instance. A marked decrease in the liver glycogen, and to a lesser degree in the muscle glycogen resulted from the administration of the extract. On autopsies no deviation from the normal microscopic appearance was found.

SUMMARY

The existence in some liver extracts of a substance capable of producing glycogenolysis, glycosuria, and hyperglycemia in the normal rat has been demonstrated. The glycogenolytic principle is water soluble, heat stable and dialysable through cellophane. It is not a protein. It is less active by mouth than parenterally. It is resistant to acid, although it loses some activity in alkali. A partial purification has been accomplished.

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Experimental Gastric Lesions Produced by Calcium Deficiency

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Rats fed a calcium deficient diet develop lesions in the antrum of the stomach that resemble certain forms of gastric ulceration in man. The pathological changes in the mucosa of the antrum consist of hemorrhagic ulcerations in areas of epithelial hyper-

plasia that tend to undergo spontaneous healing. Recurrent hemorrhage and necrosis occur in healing defects. Lesions appear after the second or third week of the deficiency but are most numerous after four weeks. When experiments are continued for eight weeks the ulcerations are larger and more hemorrhagic but do not penetrate the muscularis mucosae. Addition of calcium to the diet results in rapid repair of epithelial defects and complete regeneration of glands. Scarring does not occur within the time limits covered by these experiments. Preliminary studies on the circulation in the mucosa indicate that calcium deficiency has an effect on the capillaries.

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The Experimental Production of Recurrent Convulsive Seizures in the Monkey

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Acute, intermittent, and recurrent convulsive seizures have been induced in the rhesus monkey by the single application of discs containing various chemical and immunologically active substances to the cerebral cortex overlying the motor area. The recurrent seizures have been either Jacksonian or generalized in type and have been elicited in some animals for more than two years to date. Hydrous oxides of aluminum invariably produced recurrent seizures. Other preparations such as egg-white, typhoid vaccine, etc. were not so uniformly successful. Control preparations of aquaphor, alone or in combination with other proteins, as well as empty discs, applied to the motor cortex, failed to induce seizures in animals similarly operated.

Electric shock was used to elicit contralateral focal reactions and electroencephalographic records indicated a focus. Luminal was effective in reducing or preventing seizures. Histopathologic findings and serologic studies failed to reveal significant changes in the brain or serum of reacting as compared with non-reacting animals.

The repeated convulsive seizures which have been produced by a single application of chemical or immunologic substances to the cerebral cortex offer a means of studying further the nature of the convulsive state and its treatment.

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The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy

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Study of right ventricular hypertrophy has heretofore been unsatisfactory because of several reasons, one of which is the fact that multiple precordial leads, especially those near the sternum, are *not* in proper relation to the main muscle mass of the right ventricle.

On the basis of anatomical observations, and after an investigation of unipolar electrocardiograms in adults taken from about 30 different areas of the body, we found that the unipolar lead taken from the right upper abdominal wall is of distinct value in determining right ventricular hypertrophy, even of moderate extent.[1]

To understand how this lead is of value,

* Work done in part under a Fellowship of the Martha G. Hall Foundation.

the following explanation is necessary: the ventricles may be considered as a cup-shaped muscle mass. The wave of activation spreads through the ventricles from within, outward. Since the wave of activation has a (+) pole in the direction in which the wave is spreading, theoretically, a lead over the left ventricle should record a (+) potential; and a lead over the right ventricle should also record a (+) potential. This occurs in children where the relative sizes of the right and left ventricles are similar. In adults, the left ventricle is much larger than the right, and the right upper abdominal lead, instead of being (+) is small and iso-electric. However, when right ventricular hypertrophy occurs, the right upper abdominal lead becomes (+), even when there is no change in the electrical axis of the standard leads; and in those cases of right ventricular hypertrophy in which the precordial leads have heretofore not been characteristic.

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Ultra Violet as an Auxiliary in Eye Biomicroscopy

Georges Kleefeld

Structures of the living eye can be studied microscopically thanks to the invention of the slit lamp. The fluorescence of the eye, exposed to Wood light, retained the attention of research men, among them Hague, Feldman, and Van Lint.

In 1927, Duke Elder published the description of his ultra violet slit lamp, wherein the Nitra bulb was replaced by a mercury low pressure vapor tube. The optic lenses were made of quartz. The light was filtered by a sheet of Wood glass.

In fact, the rays of Å 3660, which are those provoking fluorescence, are not intercepted by the optic glass used for making lenses. This simplifies the problem considerably, because the average equipment can be used for the routine examination and fluorescense as well.

Since 1927 new improvements have been brought to the tubes. My research work started in 1939, so that in April 1940 I was able to show the fluorescence in the eye when exposed to the very powerful light of the high pressure mercury vapor arc. It is a tube very similar to that I used for the present research work. The power was increased by a reflector. Visible light and short ultra violet were cut off by a Corning or a pyrex filter transmitting Å 3660. It is of great importance to insist upon the fact that this light is considered as harmless. For myself, I have never suffered from exposure, nor have the persons examined.

Equipment: The ultra violet lamp is attached to a swinging arm, in order to bring the former more or less close to the patient's eye; his chin rests upon the proper part of the unit, which consists besides of a slit lamp and a binocular microscope.

Technique: The eye is always observed through the microscope; it is exposed to the light of the ultra violet lamp, or to that of the slit lamp, or to both together. Sometimes a red filter is inserted in the slit lamp beam when the last kind of examination takes place.

Some observations and results:

1. The emission of filtered light suffices for the examination of the skin, the conjunctiva, the cornea, the iris and the anterior part of the lens. It allows the removal of concretions in the conjunctiva. It provokes a pupillomotor reaction.

2. The *Dark Light* is emitted after passage through a purple filter. This filter

reflects upon the skin, the conjunctiva and the cornea, so that there is a discoloration of the latter.

3. The reports of previous observers about fluorescence of the lens, cornea and conglomerates were confirmed also.

4. In addition, the keratic precipitates are visible in ultra violet.

5. Pigment deposits laying upon the crystalloid are easily studied in U.V. and become more visible in combined light with addition of a red filter. The same is to be said about the posterior synechiae. Further observations will prove that the pigment located behind the capsule will disappear in U.V., e.g., in siderosis of the lens. When pigment of the retinal layer of the iris disappears at the iris border of the pupil, this is easily seen in U.V.

6. Foreign bodies of the cornea become obvious upon the fluorescent background of the lens, in U.V.

7. There is a pigmentation of the cornea that is not perceivable in routine slit lamp examination. Its origin has not yet been established.

Besides, the so-called "Staehli line" and the "Fleischer line" of keratoconus are much more extended than can be seen at the routine slit lamp examination.

8. As diagnostic dye stuffs, I studied fluorescein, bengal rose, magdala red, mercurochrome and rhodamine. In U.V., rhodamine draws the limits of the epitheliolysis; fluorescein alone adheres to the exulcerated places and creeps under the epitheliolysis zone; bengal rose does not fluoresce, and stains the lesion exactly; a double staining with fluorescein is thus very interesting.

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The Treatment of Burn Shock with Sodium Lactate— A Year's Experience at Babies Hospital and Harlem Hospital

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The shock syndrome which follows severe burns is accompanied by hemoconcentration and diminished plasma volume. Treatment with solutions of crystalloids has recently been supplanted by the administration of plasma and its derivatives. Further study shows that the problem is more complicated.

Recent experiments suggest that electrolytes deserve reconsideration.[1, 2] Accordingly sodium lactate has been administered to treat shock accompanying severe extensive third degree burns at Harlem Hospital and Babies Hospital.

Sodium was given orally as isotonic (1.75%) sodium lactate solution; 125 cc. per kilogram body weight given in the first 24 hours. This amount was reduced as the urinary output reached normal. In severe burns, the lactate was given by a Levine tube; occasionally isotonic sodium chloride was given intravenously for a short time to combat transient circulatory collapse. Vomiting occurred in some cases; urinary secretion usually began a few hours after treatment was instituted and azotemia and albuminuria did not occur. When the urine became alkaline on the second day, a mixture of isotonic solution of sodium lactate and sodium chloride was used.

Laboratory studies showed lowered concentration of sodium in the plasma and a reduced excretion of sodium and chloride in the urine despite the large sodium intake and copious urinary output. This discrepancy is explained by experiments with radiosodium in mice which showed the piling up of sodium in burned and traumatized tissues.

In the two hospitals there were 64 burns,

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Columbia University College of Physicians and Surgeons.

28 of which required skin grafting. There were 5 deaths: two occurred within 4 hours in burns involving over 80% of body surface, another occurred one week after the first skin grafting operation; two occurred on the second and fourth days respectively.

The results in these cases indicate that by greatly increasing the volume of interstitial fluid by administration of isotonic sodium lactate, the circulatory collapse and reduction in plasma volume can be counteracted.

The emergency use of sodium lactate in burn shock seems justified. Further studies are needed to evaluate the possible added benefit of small amounts of plasma.

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Tinnitus Aurium: Observations on Its Nature and Control

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The hypothesis on which this investigation has been based is that tinnitus is the homologue in the auditory apparatus of paresthesia in the apparatus of common sensation. It represents a paresthesia of the cochlear nerve, and is evidence of an active disease process.

If this view is correct, tinnitus and its accompanying deafness should present a clinical picture comparable with that of peripheral neuropathy and should respond to the same general principles of treatment which have been found effective in that condition.

To test this view, some clinical experiments have been made by interrupting the sympathetic pathway (stellate ganglion block, 18 cases) and by the exhibition of vasoconstrictor and vasodilator substances.

The results of these experiments will be described. They would seem to support the thesis. The results of treatment will also be described in a group of 175 patients observed over the years 1940-1943. Treatment was directed toward abolishing the assumed vascular disturbance with a vasodilator substance, nicotinic acid. Results for cases of all types show 15 per cent obtaining complete relief, 48 per cent definite improvement, a total of 63 per cent.

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Accelerated Postpartum Involution of the Uterus with Vitamin B Complex Therapy

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Observations that the liver loses its ability to inactivate estrogen in vitamin B complex deficiency, and that B complex restores this function,[1] were applied clinically to treatment of syndromes associated wtih excess estrogen (menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension).[2] Among patients thus treated, one had menorrhagia several months postpartum associated with persistent uterine subinvolution and numerous indications of nutritional deficiency; the uterus involuted rapidly on B complex therapy. Two other patients with nutritional deficiency had a history of postpartum uterine subinvolution.[2]

On the assumption that the latter condition is related to excess estrogen, owing to failure of destruction in the liver, two groups of pregnant women—all private patients—were studied. One was maintained on an average diet; the other received substantial supplements of vitamin B complex during pregnancy. All the patients were examined 6 weeks postpartum for evidence of uterine subinvolution. In the control group of 107, 6 patients had poor involution; in 23 it was fair, in 78 good and in none could it be called excellent. In the group of 76 that received B complex, none had poor involution; in 3 involution was fair, in 56 good and in 17 excellent. Thus the rate of involution was definitely enhanced in the group receiving B complex.

Recent reports emphasize the inadequacies of American diets during pregnancy. Peoples subsisting largely on whole grains customarily require shorter periods of postpartum rest than our own usual minimum of ten days. This study provides further evidence for the need of a greatly increased intake of vitamin B complex during pregnancy and the puerperium.

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The Effect of Vitamin A Supplements on the Concentration of Vitamin A in the Blood During Pregnancy

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In a previous communication[1] we have shown that during the last trimester of pregnancy there is a fall in the concentration of vitamin A in the blood whereas the carotene level is sustained. The decrease in the blood level of vitamin A is probably due to an increased demand by the fetus for this vitamin during the last 3 months of pregnancy. Analysis of the vitamin A content of the livers of 24 newborn infants has revealed considerable quantities of vitamin A.

The present study was undertaken to ascertain whether, by administering vitamin A supplements daily to pregnant women, the fall in vitamin A could be prevented during the last 3 months of pregnancy. Forty women enrolled in the Maternity Service of Beth Israel Hospital were given 10,000 units of vitamin A daily and blood levels for the vitamin were determined prior to the administration of vitamin A and, again, toward the end of pregnancy.

The results of this study revealed that the vitamin A blood level could be prevented, in most instances, from falling during the last trimester by the administration of 10,000 units of vitamin A daily. In those women whose blood levels were low prior to the administration of vitamin A the concentration of vitamin A in the blood rose following the use of the vitamin supplement.

The vitamin A blood levels of the umbilical cords were also obtained in order to determine whether the administration of vitamin A supplements during pregnancy would raise the concentration of vitamin A in the blood of newborn infants. It was found that, despite these daily supplements, the vitamin A blood levels of the umbilical vessels were not appreciably increased. Furthemore, the administration of very large amounts of vitamin A during labor (200,000 units), brought about no increase in the vitamin A blood levels in the umbilical cord although the maternal blood values were considerably enhanced. These observations would indicate that the transmission of vitaman A through the placenta is quite limited. Similar studies with the use of carotene are now being carried out.

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Pedicle Patch-Graft Pyloroplasty

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A plastic operation is described consisting of the excision of the anterior wall of the pylorus, including the sphincter and adjacent portions of the stomach and duodenum, followed by repair of the resultant defect with a viable pedicle patch-graft taken from the greater curvature of the stomach and including all gastric layers. Fifteen dogs were operated upon, nine successfully.

The stomach x-rayed three weeks after this operation empties more quickly than normal and sphincteric action by the antral (pre-pyloric) muscles is indicated.

The grafts showed satisfactory healing with no tendency toward ulceration, atrophy, out-pouching, or stenosis. The identity of the layers of the grafts was preserved histologically 3 weeks postoperatively. Those dogs which survived showed a satisfactory postoperative course over various periods of observation up to ten months.

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*Studies on the Prevention and Treatment of Experimental Renal Obstruction from Sulfadiazine**

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Therapeutic measures most commonly employed and regarded as effective at the bedside in the prevention and treatment of renal obstruction caused by sulfadiazine, consist in the "forcing of fluids" in combination with massive alkalization. This investigation represents an attempt to evaluate the merits of these clinical measures under the standard conditions of the animal experiment. It contains, in addition, an approach to some new therapeutic procedures, not yet tested clinically, concerning the dislodgment of a fully established renal block caused by intratubular precipitation of sulfadiazine.

In the *Prevention* of renal obstruction, the following method was employed: Closely bred albino rats from our own standard colony were used in all experiments. Daily stomach tube feedings of fixed amounts of water represented the "forcing of fluid." Alkalization was obtained by adding sodium bicarbonate to the water. For the purpose of comparison, two subgroups received solutions containing an acidifying instead of an alkalizing salt (sodium chloride and ammonium chloride). After standard conditions had been established, sodium sulfadiazine was injected chronically into all rats, in amounts which were known to produce invariably massive precipitation of sulfadiazine in the renal tubules, provided no therapy was employed. Throughout the experimental period which varied from 3 weeks to 9 weeks in individual tests, volume, specific gravity, pH and drug concentration of the urine were recorded daily and frequent determinations of the sulfadiazine level and nonprotein nitrogen content of the blood were also carried out. Complete post mortem examinations were performed on all animals succumbing during the experiment and also on all survivors, which were killed by exsanguination. Important organs of representative animals were studied histologically.

Chronic sulfadiazine intoxication produces in rats the most significant pathologic-anatomical changes in the kidneys, in the aorta and other parts of the arterial tree and in the thyroid gland.

The striking success of alkalization in combination with the "forcing of fluids" was clearly borne out by the high rate of

* This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

survival (no death), and the almost complete absence of significant pathological lesions in the alkali treated animals. The forcing of water alone, however, as well as the administration of acidifying salt solutions did not provide adequate protection. Animals of these groups succumbing to the sulfadiazine intoxication revealed, without exception, massive intratubular precipitation of sulfadiazine accompanied by severe tubular dilatation and degeneration of the kidneys. Apparently related to the renal impairment was the aortic damage which consisted in a necrosis of the media starting in the muscle fibers and followed by swelling and destruction of the elastic membranes and imbibition of the necrotic tissue with calcium salts. In many advanced instances the aorta assumed a bamboo-stick-like appearance, because of the segmental arrangement of bulging calcified rings, similar to the "goose's trachea" described in the medial sclerosis of Moenkeberg. True bony metaplasia developed in some cases of longer standing. The thyroid gland showed macroscopically marked increase in size and upon histological examination presented a picture of seemingly high glandular activity (as previously described by MacKenzie and MacKenzie and others).

The investigation proved that in the animal experiment intrarenal concrement formation from sulfadiazine and its serious consequences can be prevented by alkalization in conjunction with the "forcing of water."

In the *Treatment* of renal obstruction, standardized experimental conditions were established in the following manner: The renal block was produced in albino rats by intraperitoneal injection of a single fatal dose of sodium sulfadiazine. If left untreated the animals invariably developed pronounced and long-lasting renal obstruction from intratubular precipitate of sulfadiazine, and 80 per cent succumbed to this complication after 2-3 days. Treatment consisted in stomach tube feedings of fixed amounts of water or salt solutions (containing either $NaHCO_3$, NH_4Cl, a mixture of these two, or NaCl). The fluids were given twice daily, starting with the day of renal obstruction and continuing for at least one or several more days.

The most striking result was the excellent therapeutic success achieved with solutions of sodium chloride and of the mixture of $NaHCO_3$ and NH_4Cl. They made possible the complete recovery of all rats from an otherwise fatal sulfadiazine intoxication, whereas no benefits were derived from the "forcing of water" alone. The water-sodium bicarbonate combination even shortened the time of survival, and ammonium chloride, in addition to a further reduction of the life span, also increased the mortality to 100 per cent. Serum pH values obtained from heart blood indicated the presence of a severe uncompensated acidosis in the ammonium chloride group, and the development of an uncompensated alkalosis in the bicarbonate treated animals. The pH values of the other groups remained within the normal range.

From these findings the remarkable therapeutic effect of a mixture of ammonium chloride and sodium bicarbonate, in exactly the same concentrations, which when administered separately had only toxic effects, can now be explained. The combination of the alkalizing and acidifying salt in one solution will prevent dangerous changes in the acid-base balance of the body, which are so readily elicited in the presence of renal obstruction, and will thus enable the increased crystalloid concentration to initiate a powerful and life-saving diuresis (salt diuresis). This latter contention would also explain the therapeutic effect of large doses of saline solution despite its drawback of being a slightly acidifying agent.

The procedure employed in the latter investigation, represents a simple method for accurate comparative experiments on the treatment of renal obstruction from sulfadiazine.

Studies with modifications of composition, dosage and route of administration of therapeutic agents and with variations in the time of onset, frequency and duration of therapy are under way and will be reported at a later date.

*Psychological Changes in Late Post-Concussion Head Injuries**

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This is a partial report on the selection and use of tests for evaluating the relative operation of "neurotic," "diffuse organic" and "normal" mechanisms respectively responsible for the production of late post-concussional changes in dispositions and intellect following head injury. Personality and mental changes were chosen as the most promising late post-concussional complaints for investigation because they have not only a high frequency of occurrence but they are also capable of being objectively measured by psychological and psychophysiological techniques. The experimental procedure of empirical selection and careful matching of subjects in each of the three "pure" cultures or groups was used in preference to the more usual random sampling or selection technique. The method of working with "pure" subjects, well matched with reference to age, intelligence, sex, etc., provides more easily the clearcut differences in test responses needed for identifying the essential neurotic and organic mechanisms operating within the individual. The practical clinical use of the characteristic test responses thus discovered is to be in intra-individual diagnosis and not in merely determining group differences. The three experimental "pure" cultures, all of which were matched with reference to the aforementioned factors, were: 1) normal subjects without psychoneurotic reactions or head injury of any kind, 2) patients with diffuse post-concussional brain damage without any psychoneurotic features who have adjusted well in their domestic and work responses even though at a lower level, and 3) patients with clear-cut psychoneurotic features without history of head injury.

These groups were studied with a preliminary battery of 33 promising psychological tests. Six of these were finally chosen. Each of these six tests provided a measurable positive response pattern characterizing each of the 3 groups mentioned above. Slides were presented to show the occurrence of test response patterns in the individual subjects making up each of these "pure" groups. The patterns were so characteristic as to differentiate each member of a group from a member of any of the other 2 groups. The normal pattern was found to apply to subjects of superior intelligence as well as to those within the range of the experimental subjects. The pattern indicating diffuse brain damage was also found to be entirely valid in those head-injured subjects who fell above or below the limitations of intelligence and age as required by the matching criteria. In order to exhibit its method of practical clinical application the battery was applied to the usual types of head-injured cases with a mixture of organic and neurotic features. They exhibited test patterns from which the relative weights of both of these features could be estimated.

* The work described in this abstract represents a partial report on research done under a contract (Head Injury Project No. OEMcmr.-148) recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University. This project is directed by Drs. Tracy J. Putnam and John G. Lynn.